Arrhythmogenic right ventricular cardiomyopathy/dysplasia: a not so rare "disease of the desmosome" with multiple clinical presentations

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Summary

Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) is a rare but increasingly recognized form of a cardiomyopathy, involving primarily the right ventricle. Mutations in four candidate genes coding for the ryanodine receptor, and three desmosomal proteins (plakoglobin, desmoplakin, plakophylin) are known to cause the disease in some patients. Typically, the right ventricular myocardium is replaced by fibrofatty infiltrates, leading to electrical instability and ventricular arrhythmias, reduced contractility and heart failure. The left ventricle may also be involved. Unfortunately, the disease is most often diagnosed post mortem, especially in young adults dying suddenly during exercise. Since the disease is inherited in up to 50% of cases, the screening of relatives is important. The advent of the ICD revolutionized the therapeutic approach in these patients. Nevertheless, the mortality of the disease remains to be 2 - 4% per year. The presence of left ventricular involvement and a history of congestive heart failure were identified as independent risk predictors for an adverse outcome. In this paper, we describe several clinical presentations of ARVC/D, discuss the algorithm for its diagnosis and provide a review of the literature.

Introduction

Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) is a rare disease entity, characterized by progressive fibrofatty replacement of the right ventricular myocardium (Table 1). The disease was first described by Frank and Fontaine in 1978 [2] and it was recognized as a distinct cardiomyopathy eighteen years later [1]. Clinically, patients with ARVC/D mostly present with ventricular arrhythmias, ranging from ventricular ectopic beats to sudden cardiac death as the first manifestation of the disease. Progressive right or biventricular involvement may lead to terminal heart failure, necessitating heart transplantation in the most severe cases. The prevalence of ARVC/D is higher in men than in women (1.6:1) and the incidence is highest between 5 and 40 years [2]. The prevalence is estimated to range from 6/10,000 in the general population to 44/10,000 in some areas in Northern Italy [3], [4] and Germany [5]. It is inherited in approximately 50%. ARVC/D is recognized as a cause of sudden, exercise-related deaths in athletes under 35 years of age [6], [7]. It appears that sudden deaths in young athletes occur with a frequency of 1:100,000 to 1:300,000 in the United States [7], with ARVC/D accounting for about 2-3% of these deaths [8]. In Italy, however, this figure is tenfold higher [9]. This difference may be due to a different genetic background, or due to the fact that there is a unique screening program for athletes engaging in competitive sports in Italy [10]. ARVC/D also accounts for a significant number of non-exercise-related sudden deaths in the young, i.e. up to 20% both in Europe [6] and the United States [11]. In addition, ARVC/D seems to be responsible for a certain number of early and unexpected postoperative deaths [12]. If the disease is recognized in an early stage and if appropriate treatment is instituted, sudden cardiac death may be prevented in most cases. In this paper, we describe several different presentations of ARVC/D and provide a review of the literature on this rare but increasingly recognized disease.

Case Reports

Patient 1

A 20-year-old recruit of the Swiss army collapsed during a 12-minute-run. He was found pulseless, therefore basic cardiac life support was started immediately. An automated external defibrillator delivered an electrical shock based on the diagnosis of ventricular fibrillation. However, pulseless electrical activity followed. The patient was resuscitated by paramedics using repetitive administration of epinephrine and atropine. Airway protection was ensured by intubation and the patient was mechanically ventilated. As the patient was admitted to the hospital 25 minutes after the initial event, blood pressure could be measured again. At the hospital CT scans of the brain and the thorax revealed no abnormalities. A toxicology screening of the urine was negative. A 12-lead ECG was normal. Transthoracic echocardiography showed a dilated right ventricular outflow tract (Fig. 1) but was otherwise normal. However, two days after admission to the hospital, hypoxic cerebral edema developed and brain death was diagnosed. Post-mortem examination showed that the right ventricular musculature was partially replaced by fibrofatty tissue, a finding consistent with ARVC/D. His mother told later that her son had two episodes of syncope during adolescence, one shortly after running upstairs. A cardiological examination was suggested but not done.

Patient 2

A 24-year-old man lost consciousness 10 minutes after the start of a basketball game. Basic cardiac life support was performed by other players. After arrival of the emergency medical team an ECG showed asystole with occasional wide complexes. Advanced cardiac life support included intubation, mechanical ventilation and

transcutaneous pacing. Atropine and epinephrine were repetitively administered intravenously. Nevertheless, cardiopulmonary resuscitation was not successful and was stopped after one hour. The patient's history was later taken from his parents. He had never suffered from a major disease. However, two uncles died from sudden cardiac death, and two other uncles had ARVC/D. Post-mortem examination showed that the right ventricle consisted partially of fibrofatty tissue (Fig. 2), a finding consistent with ARVC/D. Electrophysiological examination of the patient's brother showed inducible sustained ventricular tachycardias, and an implantable cardioverter-defibrillator (ICD) was implanted.

Patient 3

A 51-year-old woman underwent laparoscopic abdominal surgery because of an intestinal obstruction due to a sigmoid volvulus. The initial postoperative course was uneventful. The postoperative ECG showed negative T-waves in the right precordial leads, which were thought to be due to a hypokalemia of 3.2 mmol/L. Potassium was supplemented and the patient was transferred to the ward. Four days after surgery, the patient was found unconscious and without a detectable pulse by the nurse on night shift. Cardiac resuscitation was started immediately, but careful examination showed that livores had already formed and cardiac life support was stopped. Post-mortem examination revealed a dilated, hypertrophied right ventricle. Histology showed marked lipomatosis and a disturbed texture of the right ventricular myocardium, consistent with the diagnosis of ARVC/D.

Pathology

The pathology material analyzed comes from autopsy studies and endomyocardial biopsies. The latter have to be sampled at the junction of the septum and the right ventricular free wall. Often, the biopsies are harvested from the septum, which is usually spared by the disease, and sampling errors result. The dilated right ventricle is covered by fatty tissue. There is a substantial (≥ 50%) fibrofatty infiltration of the subepicardial areas, with strands of normal or atrophied cardiomyocytes interspersed in-between (Fig. 2). The subendocardial cardiac muscle layer appears more or less normal. Fibrofatty infiltration of the His bundle and its two branches were found in 68% of ARVC/D patients [13]. However, high-degree AV-block is not a usual finding in ARVC/D patients. The thickness of the right myocardial free wall can be reduced. At a later stage, the left ventricle may also be involved in this process: In a study of 30 hearts at autopsy, left ventricular involvement was found in 47% [14].

Replacement of the RV myocardium by fibrofatty tissue is due to four basic mechanisms (Figure 3, [15]):

1. Apoptosis: Fragmented DNA and expression of protease CPP-32 are two major indicators of cellular apoptosis. Both were present in 75% of myocardial specimens from patients with ARVC/D [16].
2. Dystrophy. Due to some metabolic or ultrastructural defect, there is progressive myocyte loss. The discovery of mutations in the ryanodine receptor or in desmosomal proteins indicate that this pathogenetic mechanism may be of major importance.
3. Inflammation: Patchy inflammatory infiltrates are present in approximately two thirds of patients with ARVC/D [14]. Viral myocarditis may be important pathogenetically, at least in non-familial forms of the disease. Bowles et al. found

enteroviral or adenoviral sequences in myocardial samples in most patients with ARVC/D [17]. As the authors point out, it is not clear if ARVC/D patients are more prone to myocarditis or if myocarditis truly plays a pathogenetic role. In another study on sporadic cases of ARVC/D, myocarditis was diagnosed in 70% of 30 patients according to the Dallas criteria [18], indicating again that myocarditis involving the right ventricle is at least a major differential diagnosis of ARVC/D. On the other hand, Calabrese et al. were not able to find enteroviral genome using nested PCR technique [19]. In their study of 20 patients, 45% had a family history for ARVC/D. The negative result may in part be explained by technical problems isolating RNA.

4. Myocardial dysplasia, leading to adipogenesis and fibrogenesis. An example of maldeveloped right ventricular myocardium is Uhl's anomaly, in which the right ventricular myocardium is absent at birth already and replaced by fibrous tissue [14].

In some cases, the coronary arteries show increased thickness of the media, leading to luminal obstruction. This may explain the chest pain experienced by some patients. However, coronary artery obstruction does not play a major role in the pathogenesis of ARVC/D. The histological findings described above mirror the electrical reentrant phenomena and late potentials probably generated in the strands of cardiomyocytes within the fibrofatty tissue. However, environmental factors are important in the triggering of a life threatening arrhythmia [20]. The histological analysis of the right ventricle showing massive fibrofatty replacement of the myocardium remains a hallmark of ARVC/D. Several animal models exist, including dogs, cats, minks, and mice [21],[22],[23] to study this rare disease entity.

Genetics

In up to 50% of patients with ARVC/D a positive family history can be elicited [24]. Usually, the disease is inherited as an autosomal dominant trait with incomplete and age-related penetrance and variable forms of clinical expression. Autosomal-dominant forms of ARVC/D have been mapped to 9 different chromosomal loci by linkage analysis or direct sequencing of candidate genes (Table 2). In addition, three autosomal recessive forms of ARVC/D have been reported so far (Table 2).

Although the first ARVC/D locus was identified in 1994, progress to identify genes and their mutations responsible for ARVC/D was rather slow, but four mutated proteins have been described so far.

In ARVC/D 2, point mutations (single nucleotide polymorphisms or SNPs) were discovered in the human ryanodine receptor gene 2, and four RyR2 mutations (R176Q, L433P, N2386I, and T2504M) were identified to be transmitted from patient to patient along generations but were not detected in healthy relatives. The RyR2 protein is a tetrameric protein essential for intracellular calcium homeostasis and excitation-contraction coupling. It links to the dihydropyridine receptor of the t-tubule, thus inducing release of calcium from the sarcoplasmatic reticulum to the cytosol upon membrane depolarization. The RyR2 missense mutations may disturb the calcium channel function and trigger apoptosis and cellular necrosis. Moreover, impaired intracellular calcium release may foster electrical instability [25].

Two mutations involve the desmoplakin gene. One mutation (S299R) is transmitted as an autosomal-dominant trait (ARVC/D 8 [26]), and one as an autosomal-recessive trait inducing a distinct phenotype with woolly hair and a pemphigous-like skin disorder ([27], G2375R). Desmoplakin (DSP), in conjunction with plakoglobin (JUP), anchors to desmosomal cadherins, forming an array of nontransmembrane proteins which join keratin intermediate filaments to the plasma membrane (Fig. 4).

ARVC/D

Desmosomes serve as major cell-cell junctions, especially in epidermal cells and in cardiomyocytes [26].The S299R mutation disrupts a protein kinase C phosphorylation site at the amino-terminal domain [28]. This phosphorylation site is important for the interaction with desmosomes at the plasma membrane side as well as for binding to plakoglobin. The G2375R mutation will impair desmoplakin binding to intermediate filaments [27]. Both mutations may impair the right ventricular response to mechanical stress. Desmosomal dysfunction can lead to detachment of myocytes, with progressive apoptosis and fibrofatty replacement.

The mutation of Naxos disease, which is inherited in an autosomal-recessive fashion, involves the plakoglobin gene (Table 2). The deletion of nucleotides 2157 and 2158 causes a frameshift and premature termination of translation [29]. Thus, the C-terminal domain of plakoglobin is shortened by 56 amino acid residues.

Recently, several mutations in a gene encoding for plakophylin-2 protein(PKP2), which is also a constituent of desmosomes, have been described in ARVC/D patients [30]. Since mutations in desmosomal proteins such as PKP2, JUP, and DSP (Table 2) seem to be important in the pathogenesis of ARVC/D, the disease has been named “a disease of the desmosome” [30]. It is of interest that mutations in the regulatory domain of the transforming growth factor-β3 gene were identified recently in patients with ARVC/D 1 [31]. TGF- β3 may play a role in desmosomal protein modulation.

Clinical diagnosis

As described in the case reports, several clinical manifestations are observed. Unfortunately, the first manifestation may well be a sudden cardiac death (7-23% [4]). It may be heralded by palpitations, dizziness or even presyncope or syncope often related to physical exercise. These symptoms are due to ventricular arrhythmias and require further investigation. Very rarely, patients may complain of chest discomfort

or anginal pain on exertion. The patients are usually young (33 ±14 years, range 13-73 [15]), with a male predominance. In patients with less arrhythmogenic forms of the disease, symptoms and signs of heart failure may be the first presentation. Sometimes it will be difficult to make a differentiation from other cardiomyopathies. Physical examination may be normal in about 50% of patients. A wide splitting of S2 due to delayed pulmonic closure secondary to RV dysfunction may be present [32]. Tricuspid regurgitation murmur is sometimes observed, as well as an S3 gallop due to right ventricular failure.

The major and minor criteria to diagnose ARVC/D are depicted in Table 1. Basically, global and/or regional dysfunction and structural alterations of the right ventricle should be documented by an imaging modality. ECG criteria include the presence of T-wave inversions in right precordial leads V2 and V3 with localized prolongation of the QRS complex (>110ms), Epsilon waves, and arrhythmias such as ventricular extrasystoles or ventricular tachycardias with LBBB morphology (Table 1). The propensity for arrhythmias may be quantitated by documentation of late potentials on signal-averaged ECG. An endomyocardial biopsy to show replacement of the right ventricular myocardium by fibrous or fatty tissue is only rarely performed because of possible sampling errors and the inherent complication rate of the procedure. A diagnosis of ARVC/D is made if either 2 major, 1 major and 2 minor, or 4 minor criteria are present, respectively (Table 1).

In a retrospective analysis of 130 patients Hulot et al.[33] showed that the natural history of the disease may be diverse. The overall mortality rate was 18.5% and the annual mortality rate was 2.3%. Mean age at death was 54 ± 19 years. The most important cause of death in this study cohort was progressive heart failure (59%) with sudden death being less frequent (29%). The documentation of ventricular tachycardias and clinical signs of right ventricular failure and/or left ventricular

dysfunction were risk factors for cardiovascular death.

It remains a challenging task to predict which patients are at a high risk for sudden cardiac death. Established risk factors are (i) diffuse involvement and enlargement of the right ventricle, (ii) involvement of the left ventricle, (iii) impaired function of the right (and left) ventricle, and (iv) the presence of sustained ventricular tachycardias, induced during programmed electrical stimulation, when associated with an enlarged and dysfunctional right ventricle [4].

At the University Hospital Zurich, Switzerland, sixty-one patients (mean age 44 $\pm$ 14 years; 44 males) were diagnosed with ARVC/D based on standardized diagnostic criteria [34]. Among 41 patients who underwent electrophysiologic stimulation, 27 had an inducible sustained monomorphic ventricular tachycardia. Medical treatment included beta-blockers in 41 patients, sotalol in 19 patients, and amiodarone in 16 patients. Twenty-four (39%) patients received an implantable cardioverter defibrillator (ICD) during follow-up. During a mean follow-up period of 55 $\pm$ 47 months, ten patients with ARVC/D died. The annual rate of death in this patient cohort was 4%. The cause of death in eight patients was likely to be arrhythmic (sudden cardiac death; one of the patients had an ICD) and two patients died from advanced heart failure (one patient with ICD). Five patients underwent heart transplantation due to terminal heart failure. Risk factors significantly associated with adverse outcome (defined as sudden cardiac death, death from heart failure or need for heart transplantation) were a history of congestive heart failure ($p<0.001$), the presence of left ventricular involvement on echocardiography ($p<0.001$), left atrial dilatation ($p<0.05$), prolonged PR duration ($p<0.01$), prolonged QRS in V_1 ($p<0.05$), and bundle branch block ($p<0.05$). In a multivariate analysis, a history of congestive heart failure and the presence of left ventricular involvement were identified as independent risk factors for an adverse outcome.

Evaluation of relatives

Relatives of deceased patients often ask for a work-up to make sure that they are not carriers of the disease. Theoretically, the same criteria listed in Table 1 are used to screen relatives for the presence of the disease. However, Hamid et al. proposed that the original criteria [35] should be modified [36]: The original criteria are highly specific but not sensitive enough to evaluate relatives who may have an early form of the disease. Therefore, they suggested that in first-degree relatives of patients with known ARVC/D any minor criterion listed in Table 1 will indicate familial involvement. In addition, they recommended that 200 instead of 1000 ventricular extrasystoles in a 24 hour electrocardiogram constitute a criterion to diagnose the disease in this context. When these modified criteria are used to screen relatives, 39% of them will have signs of the disease, as opposed to 28% if the original criteria were used [36]. A similar percentage (41%) was reported by Nava et al. [37]. During a long-term follow-up (mean 8.5 years) of 37 Italian families encompassing 365 subjects, Nava et al. reported a favorable prognosis even for affected patients (mortality rate of 0.08 patients/year) [37]. Despite this fact, diligent medical care of these patients is of utmost importance and they should avoid strenuous physical activity. Screening of first-degree relatives of patients with ARVC/D should include a medical history, a thorough physical examination, a standard 12-lead and a 24-hour ECG, a signal-averaged ECG with 40mHz filter, a bicycle stress test, a transthoracic echocardiography, a cardiac MRI, and, if high-risk features such as palpitations, syncope, nonsustained or sustained ventricular tachycardias are present, an electrophysiological study.

Screening of athletes

ARVC/D is responsible for up to 20% of sudden deaths in young people, especially

for sudden deaths related to exercise[38]. Therefore, athletes wishing to engage in competitive activities should be screened [39]. Questions to determine (i) if the individual has had effort-related chest pain, shortness of breath or syncope, (ii) if there is a family history of premature death, and (iii) if the patient has had elevated blood pressure or is known to have a heart murmur [40],[41] should be asked. Two of the three screening questions are especially relevant regarding the diagnosis of ARVC/D. A thorough physical examination as well as a 12-lead ECG is recommended before engaging in competitive sports [39]. However, distinctly abnormal ECGs can be found in healthy athletes performing endurance sports, e.g. cycling, cross-country skiing, rowing etc. [42]. 27 of 145 “distinctly abnormal” ECGs of 1005 Italian athletes showed marked repolarization abnormalities, including T-wave inversions in V1-V4 in 16 of the 27 patients. None of them had clinical features or imaging studies supporting a diagnosis of ARVC/D. Even if echocardiography should probably not be performed in every athlete because it is not considered cost-effective by some authorities [39], [8] it should be done in persons suspected to have structural heart disease. If ARVC/D is suspected clinically, further tests must be performed. A diagnosis of ARVC/D clearly precludes engagement in competitive sports [38],[43,44], because physical exercise may trigger ventricular arrhythmias in patients with ARVC/D [45]. Noncompetitive sports activities such as bowling, golf, and brisk walking are permitted [46].

ARVC/D and perioperative deaths

Tabib et al. reported a series of 50 patients who died postoperatively after low-risk surgery [12]. In 18 of these patients (36%, mean age 30 ± 16 years) an ARVC/D was diagnosed. Four patients died during induction of anesthesia, nine during surgery and three within 2 hours postoperatively. In 19 out of 200 patients with ARVC/D who

died unexpectedly and suddenly, death occurred perioperatively, indicating that these patients may be difficult to resuscitate [13]. The authors speculate that perioperative stress or drugs may trigger arrhythmias. Our case shows that death may occur even four days after the operation. Preoperative screening should include an ECG [47] and a chest X-ray even in younger patients. Special attention should be given to patients with a positive family history for sudden cardiac death.

Electrocardiogaphy

Standard 12-lead ECG

The 12 leads ECG will be abnormal in 70% of the patients [32]. As shown in Fig. 5, negative T waves are often present in leads V1-V3, sometimes extending to V5 or V6, especially in patients with left ventricular involvement. The duration of the QRS complex is often prolonged to ≥ 110ms. This prolongation of the QRS complex may be restricted to the right precordial leads V1-V3 [5]. In fact this differential prolongation of the QRS complex, defined as QRS duration in (V1+V2+V3) / (V4+V5+V6) ≥ 1.2, has a sensitivity of 98% and a specificity of 100% to diagnose ARVC/D [5]. In addition, a new electrocardiographic marker for delayed right ventricular activation was recently described: The S-wave upstroke in leads V1 through V3, measured from the nadir of the S wave to the isoelectric baseline is prolonged to ≥ 55ms in patients with ARVC/D without right bundle branch block [48]. This finding was the most prevalent ECG sign in patients with ARVC/D and also helped distinguish ARVC/D from benign forms of right ventricular outflow tract tachycardias. Moreover an epsilon-wave can be found in the right precordial leads, which corresponds to the asynchronous depolarization of the right ventricle. The epsilon-wave occurs after the QRS complex at the beginning of the ST-segment and consists of a small amplitude potential

(afterdepolarization). Using standard recording techniques a ε-wave will be found in a quarter of patients with ARVC/D. According to Fontaine, any potential in V1-V3 exceeding the QRS duration in V6 by more than 25ms should be considered an epsilon-wave [15]. Again in 25% of the patients elevations of the ST segment in right precordial leads are present, usually with upward convexity. In contrast, patients with a ST-segment elevation of coved or saddle-back type are likely to have the Brugada syndrome [49].

Interestingly, duration and interlead variability of the QT interval and the QRS complex are greater in sudden death victims of ARVC/D compared to healthy controls and patients with milder forms of the disease [50]. A QRS dispersion ≥ 40ms has a sensitivity and specificity of 90% and 77%, respectively, to predict sudden death. The increased QRS dispersion results mainly from the localized prolongation of the QRS complex in right precordial leads. Also, a QT dispersion > 65ms has a sensitivity of 85% and a specificity of 75% to predict sudden death [50].

24-hour Holter ECG

The 24-hour Holter ECG may reveal frequent multiple ventricular premature beats, i.e. >1000 per day, with a predominant LBBB morphology. In addition, nonsustained or sustained ventricular tachycardias with left bundle branch block (LBBB) morphology may occur. These two findings constitute two important minor criteria in the diagnosis of ARVC/D. Ventricular ectopic beats with a right bundle branch block (RBBB) morphology suggests left ventricular involvement.

Exercise testing

Careful analysis of arrhythmias during exercise is important, because ventricular tachycardias may be precipitated. The ventricular tachycardias with LBBB

morphology should be differentiated from the more benign right outflow tract ventricular tachycardias, which usually are found in patients without underlying cardiomyopathy. The right ventricular outflow tract ventricular tachycardias typically show an inferior axis orientation in the extremity leads (positive QRS vector in II, III, avF and negative QRS vector in aVL). In patients with ARVC/D this same axis is only observed, when the VT originate in the pulmonary infundibulum. More typically, there is a left axis deviation, because the majority of VT arises from the inferior wall or near the apex in patients with ARVC/D. The ventricular tachycardias with a superior axis are more frequent in patients with more extensive disease [51]. For a reliable differentiation of right ventricular outflow tract tachycardias from arrhythmias in patients with ARVC/D an electrophysiological study may occasionally be necessary[52], [53].

Signal averaged ECG

The value of signal averaged ECG in ARVC/D is controversial [15]. It is used to detect delayed afterdepolarizations (“late potentials”). They mirror the presence of slowed electrical propagation in the myocardium, resulting in delayed ventricular activation. The presence of slowed ventricular activation provides a substrate for reentrant arrhythmias [54]. Late potentials on signal-averaged ECG recordings are a minor criterion for the diagnosis of ARVC/D (Table 1). Late potentials on the signal-averaged ECG are the counterpart of the epsilon waves recorded on the surface ECG. Consistent with other ECG abnormalities in ARVC, the abnormalities on signal-averaged ECG are more prominent in the right precordial leads than they are in the left precordial leads. More extensive forms of the disease usually have more late potentials. Between 50% and 80% of patients with ARVC/D and sustained VT have

an abnormal signal-averaged ECG. Nava et al. examined 138 patients with ARVC/D and found that the signal-averaged ECG was abnormal in 57% of patients and 4% in healthy controls, and calculated a sensitivity of 57%, a specificity of 95%, and a positive predictive value of 92% [51]. The signal-averaged ECG may be normal if the disease is localized to a small segment of the RV, but such patients are not immune to malignant arrhythmias. Abnormal signal-averaged ECG recordings are more common in patients with more severe myocardial fibrosis and reduced RV ejection fraction [55] and predict sustained VT among ARVC/D patients with prior nonsustained VT. A filtered QRS duration of > 110ms had the highest utility in identifying ARVC/D patients prone to inducible monomorphic VT's on programmed electrical stimulation [54]. Signal-averaged ECGs should not be used in patients with QRS duration ≥ 120ms in the standard 12-lead ECG, as occurs in 20-30% of patients with ARVC/D.

Echocardiography

The right ventricle is more difficult to examine than the left. This is explained in part by its retrosternal location, and in part by its more complex geometry. Nevertheless, it must be examined in a systematic way [56], including the right ventricular inflow tract (RVIT), the right ventricular body (RVB), and the right ventricular outflow tract (RVOT). A protocol may be downloaded from the internet (http://anpat.unipd.it/ARVC). The goal of the examination is to measure the right ventricular dimensions, to quantify the function of the right ventricle, and to visualize the typical hallmarks of the disease (Fig. 6). Because the left ventricle may not be spared by the disease, it is equally important to examine the left ventricle. In fact, left ventricular wall motion abnormalities can be found in up to 25% of ARVC/D patients [57]. The three regions of the right ventricle, i.e. RVIT, RVB, and RVOT, can be

visualized as follows [58]. All measurements are obtained at end-diastole:

RVIT: From the standard parasternal long axis view the transducer is shifted to a point midway between the parasternal edge and cardiac apex. The transducer should then be tilted medially and downwards to obtain a view of the RVIT (normal mean value: 4.5cm, range 3.7-5.4), and the RVB (anterior and inferior wall, apex). It is important to exclude the RVOT from this view. The measurement of RVIT from this view is the most easily and consistently obtainable one. The RVIT can also be measured in the classical four chamber view or in a subcostal view.

RVOT: The dimension of the RVOT can be measured by M-mode at enddiastole in the standard parasternal long axis view (normal values: 0.9-2.6cm, mean 1.7cm [59], [59,60]). The dimension of the RVOT should also be quantified in the parasternal short axis view at the aortic root level (normal mean value: 2.5±0.4 cm, range 1.8 - 3.4 [61], Fig. 1). In a study of 29 patients with ARVC/D, dilatation of the RVOT was the most common and consistent finding. An RVOT diameter of >3.0cm measured in the parasternal long axis view had a sensitivity of 89% and a specificity of 86% for the diagnosis of ARVC/D [60].

RVB: The dimensions of the RVB are best measured in the apical four chamber view. The diastolic length of the right ventricle from the apical endocardial border to the tricuspid annulus is 7.1±0.9cm, range 5.5-9.1). The longest distance between the septal and lateral free wall endocardium in a plane perpendicular to the right ventricular long axis is 3.0±0.5cm, range 2.1-4.2. Qualitatively, the degree of RV dilatation should be quantitated in relation to the left ventricle (mild: RV enlarged but area less than LV area; moderate: RV area equals LV area; severe: RV larger than

LV area). In an echocardiographic study of 15 patients with ARVC/D, cavity dimensions of RVOT, RVIT, and RVB were significantly larger compared with healthy controls [62].

In ARVC/D patients, the right ventricular wall may be locally thickened or thinned. The normal RV wall thickness is defined to be 2.4±0.5mm [63]. In normal subjects the thickness of the RV wall does not exceed 4mm [58].

Regional wall motion abnormalities of the RV

For the purpose of analyzing wall motion abnormalities, three walls of the right ventricle can be differentiated: the inferior or diaphragmatic wall, the ventricular septum and the free wall [64]. The parasternal long axis view of the RVIT described above shows the inferoposterior wall directly underneath the tricuspid valve. This is the most important region to be examined, because it is frequently affected by ARVC/D. The lateral free wall of the right ventricle is best seen in the apical four chamber view. The right ventricle can also be subdivided in up to 12 segments, and each segment can be classified according to a score system: 0, not visualized; 1, normal; 2, mild hypokinesia; 3, severe hypokinesia; 4, akinesia; 5, dyskinesia; 6, isolated sacculations, bulges or outpouchings [57], [62]. In patients with ARVC/D right ventricular wall motion abnormalities are the most frequent echocardiographic findings, being present in over 70% [57], [62].

Right ventricular function

Because of the complex right ventricular geometry, the function of the RV cannot be reliably quantitated by planimetry. Using two-dimensional echocardiography, Kaul et al. reported that the RV annular motion correlated with the RV ejection fraction measured by radionuclide ventriculography [65]. More recently, RV function was

assessed by M-mode echocardiography measuring tricuspid annular movement. The M-mode cursor is directed to the lateral insertion of the tricuspid valve in the four-chamber apical view. The normal value of the annular motion at the lateral tricuspid annular position is 2.5 ± 0.4 cm [62]. In a group of 15 patients with ARVC/D, tricuspid annular motion in the lateral position was significantly decreased compared with healthy subjects (2.2 vs. 2.6 cm, $p < 0.01$ [62]). Moreover, tricuspid annular velocities can be assessed by pulsed tissue Doppler analysis.

MRI

This technique is very important in the diagnosis of ARVC/D because both cardiac structure *and* function can be evaluated [66]. Using MRI, RV function, size, global or regional wall motion abnormalities, myocardial thinning and reduced systolic thickening can be quantitated. It is also possible to visualize the fibrofatty infiltration of the right ventricular myocardium. Technical requirements are a 1.5-T scanner with a cardiac phased-array surface coil for radiofrequency signal detection. If the patient has frequent extrasystoles, a betablocker should be administered prior to the investigation [66]. For ECG-gated image acquisition, a double inversion recovery (blood suppression) fast spin-echo sequence should be used and the patient instructed to hold breath to minimize artifacts. Fat has the brightest signal intensity with the ECG-gated spin-echo technique and the MRI is the best noninvasive technique to outline the infiltration of the RV myocardium with fat [32]. Several protocols for an MRI examination of the heart in persons with suspected ARVC/D have been published [66], [67], [68]. In a retrospective analysis of 36 patients Keller et al. reported a sensitivity of 89%, a specificity of 82%, a positive predictive value of 84%, and a negative predictive value of 88% to diagnose ARVC/D with MRI examination. The most important parameter in their study was (transmural) fatty tissue infiltration of the RV

[67]. This finding was confirmed in a prospective study. Quantitative analysis showed that RV enddiastolic diameter and outflow tract area were significantly higher, and RV ejection fraction lower in ARVC/D patients compared to controls [66]. Using less dedicated software, the presence of fatty infiltration of the right ventricular myocardium may be less reliably detected [68]. Moreover, even in normal individuals epicardial fat is usually present and tongues of epicardial fat may extend into the RV myocardium [68]. ARVC/D patients, but not normal individuals, have fibrosis of the RV as well as fatty infiltrates, which both may be detected by MRI [69]. The main role of cardiac MRI is probably its use as a screening tool for ARVC/D in relatives of patients with the disease and as a means of follow-up on ARVC/D patients [70]. It is not the gold standard method to diagnose ARVC/D.

The exact role of the MRI examination in the diagnosis of patients with idiopathic right ventricular outflow tract tachycardias with LBBB morphology remains to be determined. [15], [71], [68].

Contrast ventriculography and endomyocardial biopsy

Right ventricular ventriculography used to be the gold standard for the diagnosis of ARVC/D. Fontaine et al.[15] suggested to obtain two orthogonal views of the RV (45° RAO, 45° LAO) and the use of digitized technique with 25 images/s to ensure optimal analysis and use of an angled 150° pigtail catheter. The main findings are schematically depicted in Fig. 6. In addition, the global and regional functions and the size of the RV must be quantitated. Slow evacuation of dye will be observed in areas rich in aneurysms and fissures and poor contractile function.

Examination of the left ventricle will reveal abnormalities in 20-50% of ARVC/D patients. Most often, a mildly reduced LV systolic function will be found. It should be noted that a normal RV angiogram does not rule out ARVC/D. Hebert et al examined

85 patients with ARVC/D and reported that 68% had normal right ventricular function [72]. In their study, tricuspid annulus plane systolic excursion positively correlated with right ventricular function. If it was less than 12mm it identified patients with an RV ejection fraction < 35% with a sensitivity of 96% and a specificity of 78%. Endomyocardial biopsies to confirm fibrofatty infiltration should be done at the junction of the septum and the free wall. The sensitivity was reported to be 67% with a specificity of 92% [15]. Often, the interventricular septum is not involved in the disease, and sampling errors may occur. Biopsy of the free wall of the RV carries a substantial risk of perforation. Therefore, endomyocardial biopsy cannot be recommended as a routine procedure.

Electrophysiological testing with programmed electrical stimulation

An intracardiac electrophysiological study with programmed ventricular stimulation should be reserved for symptomatic patients with sustained VT of VF, patients with syncopal episodes in whom non-invasive evaluation was negative, and asymptomatic patients with a family history of premature sudden death or non-sustained ventricular tachycardias and depressed right ventricular function (Fig. 7 [73]). The goals of the electrophysiologic study are: (i) to quantitate the potential to develop malignant arrhythmias, such as sustained VF and VF, (ii) to measure the hemodynamic consequences of these malignant arrhythmias, (iii) to evaluate the success of drug treatment on inducibility of arrhythmias and (iv) to establish the susceptibility of VT to be interrupted by antitachycardia stimulation before ICD implantation, and (v) to establish the basis for a radiofrequency ablation of a potential arrhythmic focus [74]. The value of the electrophysiologic study for risk stratification in patients with ARVC/D is not known, however. Yet another key function of the invasive electrophysiological evaluation is to differentiate the usually benign right ventricular

outflow tract tachycardia from ARVC/D. In patients with ARVC/D, the arrhythmias are usually inducible with critically timed extrastimuli, indicating a reentrant mechanism of the ventricular tachycardia. Moreover, in ARVC/D patients the ventricular tachycardias often show more than one morphology. In addition, fragmented potentials are more likely to be present in ARVC/D patients [52], [53]. In contrast, right ventricular outflow tract tachycardias are generally not associated with a progressive condition, are seldom the cause of arrhythmic death, and are not known to be transmitted genetically.

Therapy

Medical Therapy

In the acute setting, treatment of a ventricular tachycardia should follow standard procedures. Synchronized electroconversion with 200 J using unipolar electrodes is performed in the presence of low blood pressure due to the tachycardia. Patients in cardiogenic shock and a very fast tachycardia will need unsynchronized defibrillation. Various drugs have been investigated to suppress the sometimes life-threatening arrhythmias of ARVC/D including betablockers, sotalol, and amiodarone [75]. The most efficacious drug seems to be sotalol with an overall efficiency rate of 68% and 83% to treat both inducible and noninducible ventricular tachycardia in ARVC/D [75]. However, due to the progressive nature of the disease, arrhythmias may recur despite initial success of the medication. Blomstrom-Lundqvist et al. reported a 20% mortality in their group of 15 patients followed-up for 9 years [76]. These sobering numbers plus the fact, that non-inducibility of ventricular tachycardias during electrophysiologic studies does not rule out the occurrence of sudden death, led to the investigation of ICD therapy in ARVC/D patients. In patients suffering from symptoms and signs of heart failure, drug therapy including ACE-inhibitors/angiotensin receptor blockers, diuretics, and betablockers is adequate. This treatment may prevent progression of the disease, but further studies are necessary to address this issue. Patients with a dilated right ventricle and severely compromised function will need anticoagulant therapy as well.

Radiofrequency catheter ablation

Ventricular arrhythmias can be ablated with a high success rate in patients with RVOT tachycardia, but with limited success and a high recurrence rate in ARVC/D

patients [52], [74]. This treatment may have more side effects (penetration of wires and leads) because of the diseased myocardium in ARVC/D. It should be tried in patients with very frequent ventricular tachycardias or in patients who cannot tolerate medical therapy. Late relapses occur because of the progressive nature of the disease [32]. Radiofrequency ablation may be considered in ARVC/D patients who have frequent and drug-refractory VT after ICD implantation [73].

ICD

The experience with ICD therapy in patients with ARVC/D has been reported only recently and seven series have been published so far (Table 3). The implantation of an ICD device can effectively terminate life-threatening arrhythmias in patients with ARVC/D and should be considered standard therapy for these patients. However, several caveats need to be stated: Due to the progression of the disease, undersensing ultimately occurred in 13% of patients in the series by Wichter [77] requiring surgical revision or implantation of additional leads. The risk of perforation of the thinned right ventricular wall may increase over time. Other lead problems included insulation failure, fracture, dislodgment, thrombosis, or infection. It is not surprising, therefore, that late complications occur in 21% of patients receiving ICD therapy (Table 3). In addition, inadequate ICD therapies are not uncommon. To diminish the frequency of both appropriate and inappropriate ICD shocks, there is a need for concomitant antiarrhythmic therapy including betablockers in 77% of patients (Table 3).

The question which patients will benefit most from ICD therapy is not settled yet. Accepted indications for ICD therapy are (i) resuscitated sudden death and (ii) sustained ventricular tachycardias. Also, patients who have suffered a syncope with probable arrhythmogenic etiology should be considered for ICD implantation

(secondary prevention). It remains unclear, which patients with ARVC/D will require an ICD therapy for primary prevention of sudden cardiac death [78] and if the therapy should be offered for relatives with a high risk profile (inducibility of fast ventricular tachycardia during electrophysiologic study). According to Hodgkinson et al., patients with the presence of a high-risk DNA haplotype, and/or obligate carrier status by pedigree analysis, had a 28% reduction in mortality if an ICD was implanted for primary prophylaxis [78], indicating that genetic testing has a role in identifying patients at risk. Physicians are encouraged to register their patients in the European or the North American Registries (http://www.arvd.com or http://www.arvd.org [79]or http://anpat.unipd.it/ARVC [80]). An informative website on ARVC/D can also be found at http://telethon.bio.unipd.it/ARVDnet.

Table 1

Proposed clinical criteria for the diagnosis of ARVC/D [35], [24], [2]

Criteria	Major	Minor
Global and/or regional dysfunction and structural alterations of the RV†	Severe dilatation and reduction of RV ejection fraction with no or mild LV impairment Localized RV aneurysms Severe segmental dilatation of RV	*Mild global RV dilatation and/or ejection fraction reduction with normal LV function* *Mild segmental dilatation of RV* *Regional RV hypokinesia*
Tissue characterization of walls	Fibrofatty replacement of myocardium on endomyocardial biopsy	
Repolarization abnormalities		*Inverted T waves in right precordial leads V2 and V3* (patient aged >12 years, RBBB absent)
Depolarization/conduction abnormalities	Epsilon waves or localized prolongation (110ms) of the QRS complex in precordial leads (V1 or V2 or V3)	*Late potentials (signal averaged ECG)*
Arrhythmias		*LBBB type VT* (sustained or non-sustained) (ECG, Holter, exercise testing) *Frequent ventricular extrasystoles with LBBB morphology* (≥ 1000 [*>200*] / 24 h) (Holter)
Family history	Familial disease confirmed at surgery or autopsy	Familial history of premature sudden death (age < 35 years) due to suspected RV dysplasia Familial history (clinical diagnosis based on present criteria)

Table 1, continued

RV=right ventricle, LV=left ventricle, VT=ventricular tachycardia

†Detected by echocardiography, radionuclide scintigraphy, magnetic resonance imaging, or ventriculography

For the diagnosis of ARVC/D 2 major, 1 major plus 2 minor, or 4 minor criteria are required, respectively.

To screen relatives for familial ARVC/D the following modification has been suggested: ARVC/D in first-degree relative plus one of the criteria listed above in italics [36].

Table 2

Chromosomal loci and candidate genes in ARVC/D

ARVC/D Type, Reference	OMIM™ number	Chromosome Locus	Gene	Mode of inheritance	Protein	Phenotype	Country of origin
ARVC/D 1 [81, 82]	107970	14q23-q24		autos.-dom.		Classical ARVC/D	Italy
ARVC/D 2 [83, 3, 84]	600996	1q42-q43	RyR2	autos.-dom.	Human cardiac ryanodine 2 receptor	Effort-induced polymorphic VT's, RV apical aneurysm	Italy
ARVC/D 3 [85]	602086	14q12-q22		autos.-dom.		Classical ARVC/D	Italy, Slovenia, Belgium

Table 2, continued

ARVC/D Type, Reference	OMIM™ number	Chromosome Locus	Gene	Mode of inheritance	Protein	Phenotype	Country of origin
ARVC/D 4 [86]	602087	2q32		autos.-dom.		Localized involvement of LV (in addition to RV)	Italy, U.S.A.
ARVC/D 5 [87]	604400	3p23		autos.-dom.		Incomplete penetrance, late onset of disease	Canada
ARVC/D 6 [88, 89]	604401	10p12-p14		autos.-dom.		High incidence of sudden death, early onset of disease	U.S.A. (Anglo-Saxon)

Table 2, continued

ARVC/D Type, Reference	OMIM™ number	Chromosome Locus	Gene	Mode of inheritance	Protein	Phenotype	Country of origin
ARVC/D 7 [90]	--	10q22		autos.-dom.		Skeletal muscle disease	Sweden
ARVC/D 8 [26]	607450	6p24	Desmoplakin (DSP)	autos.-dom	Desmoplakin	No hair or skin alterations	Italy
ARVC/D 9 [30]	609040	12p11	Plakophyllin-2 (PKP2)	Autos.-dom.	Plakophyllin-2	Incomplete penetrance. Classical ARVC/D	Western European descent
Naxos Disease [91],[29]	601214	17q21	Plakoglobin (JUP)	autos.-rec.	Plakoglobin	Palmoplantar keratoderma, woolly hair	Greece

Table 2, continued

ARVC/D Type, Reference	OMIM™ number	Chromosome Locus	Gene	Mode of inheritance	Protein	Phenotype	Country of origin
Carvajal Syndrome [92], [27]	125647	6p24	Desmoplakin (DSP)	autos.-rec.	Desmoplakin	Pemphigous-like skin disorder, woolly hair. No fibrofatty replace-ment of myocardium. Left ventricular involvement.	Israel (Muslim-Arab origin), Ecuador
NN [93]	115650	14q24-qter		autos.-rec.		Anterior polar cataract	Argentina

NN = No name given so far. OMIM™ = Online Mendelian Inheritance in Man (http://www.ncbi.nlm.nih.gov/Omim/)

Table 3

ICD therapy in ARVC/D

Author	Years	Number of patients and gender	Mean age, years (range)	F/U, months (mean ± SD)	Primary prevention (%)	Patients on antiarrhythmic drugs at hospital discharge (%)	Time to first ICD therapy, months (range)	Appropriate ICD therapy during F/U (%)	Inappropriate ICD therapy during F/U (%)	Deaths/ HTx during F/U (%)	Late complications (%)
Wichter [77]	1991-2002	60, 49 m, 11 f	43 (14-70)	80±43	7	54	4.1 (0.3-41.4)	60	23	13/3	45
Roguin [94]	1991-2002	42, 22 m, 20 f	36 (6-69)	42±26	40	97	9 (0.1-66)	78	24	2/2	14
Corrado [95]	1992-2001	132, 93 m, 39 f	40 (15-72)	39±27	22	83	22 (2-96)	48	16	3/2	14
Hodgkinson [78]	N/A	48, 30 m, 18 f	18 (15-56)	20	73	83	35 (0.5-61) in males	47 in males	10	0/10 in males, 0/0 in females	6

ARVC/D

Author	Years	Number of patients and gender	Mean age, years (range)	F/U, months (mean± SD)	Primary prevention (%)	Patients on antiarrhythmic drugs at hospital discharge (%)	Time to first ICD therapy, months (range)	Appropriate ICD therapy during F/U (%)	Inappropriate ICD therapy during F/U (%)	Deaths/ HTx during F/U (%)	Late complications (%)
Link [96]	1992-1995	12, 7 m, 5 f	31 (15-48)	22 ± 13	0	58	N/A	67	33	8	25
Tavernier [97]	N/A	9, 8 m, 1 f	36 (11-36)	32 ± 24	0	89	N/A	78	44	0/11	N/A
Breithardt [98]	1990-1993	18	N/A	17 ± 11	0	N/A	N/A	50	N/A	N/A	N/A

m=male, f=female, N/A=not available, F/U=follow-up

Figure legends

Fig. 1

Echocardiographic parasternal short axis view. The right ventricular outflow tract ($RVOT_4$) is dilated (at arrow 5cm [normal value: 1.8-3.4cm], Case 1). RA = right atrium, Ao = aortic valve, PA = pulmonary artery.

Fig. 2

The macroscopic aspect of the right ventricle shows replacement of the myocardium by fat and fibrous tissue. Strands of myocardium are visible within the fibrous-fatty tissue.

Fig. 3

Pathogenesis of ARVC/D. RV = right ventricular. See text for details.

Fig. 4

Molecular model of the desmosome (reprinted with permission from [99]). The interaction between desmoglein and desmocollin, two desmosomal cadherin proteins, is crucial for the intercellular coherence. The desmoplakin, plakophilin, and plakoglobin proteins are important for the linkage of intermediate filaments to the cell membrane (its double layer is shown in black). The red dots show known mutations in ARVC/D patients.

Fig. 5

Typical ECG of a patient with a diffuse form of ARVC/D [48]. Note the T-wave inversions (TWI) in leads V1-V5. An epsilon-wave is seen (notch or slurring of small

amplitude in the ST transition zone indicating prolongation of the depolarization phase, vertical arrow). The QRS complex duration in leads V1-V3 is slightly longer than in lead V6. Moreover, there is prolongation of the S-wave upstroke in V1 through V3 of >55ms (reproduced with permission).

Fig. 6

Schematic drawing of a 45° right anterior oblique projection obtained during right ventricular (RV) cineventriculography. The diagnosis of ARVC/D is based on the presence of segmental morphologic abnormalities and wall motion abnormalities. The localized lesions are often present in the triangle of dysplasia, consisting of the pulmonary infundibulum, the anterior right ventricular wall including the apex, and the inferior wall including the subtricuspid area. The reduced contractility with slow evacuation of contrast material and the dilatation of the right ventricle, which is a frequent feature of ARVC/D, are not shown [15]. The hyperreflective moderator band is an echocardiographic finding [60].

Fig. 7

Treatment strategy suggested for high-risk ARVC/D patients. See text for details.

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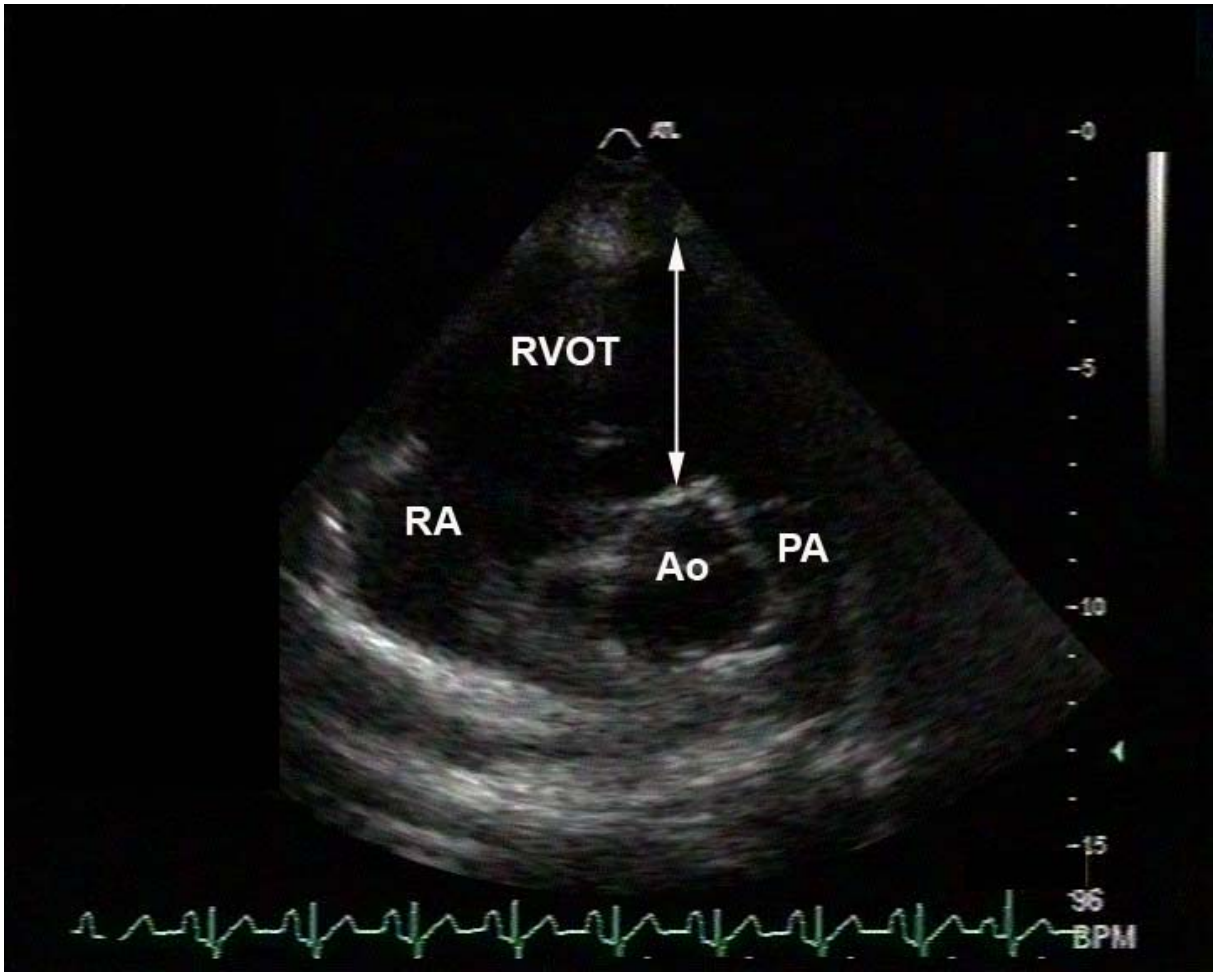
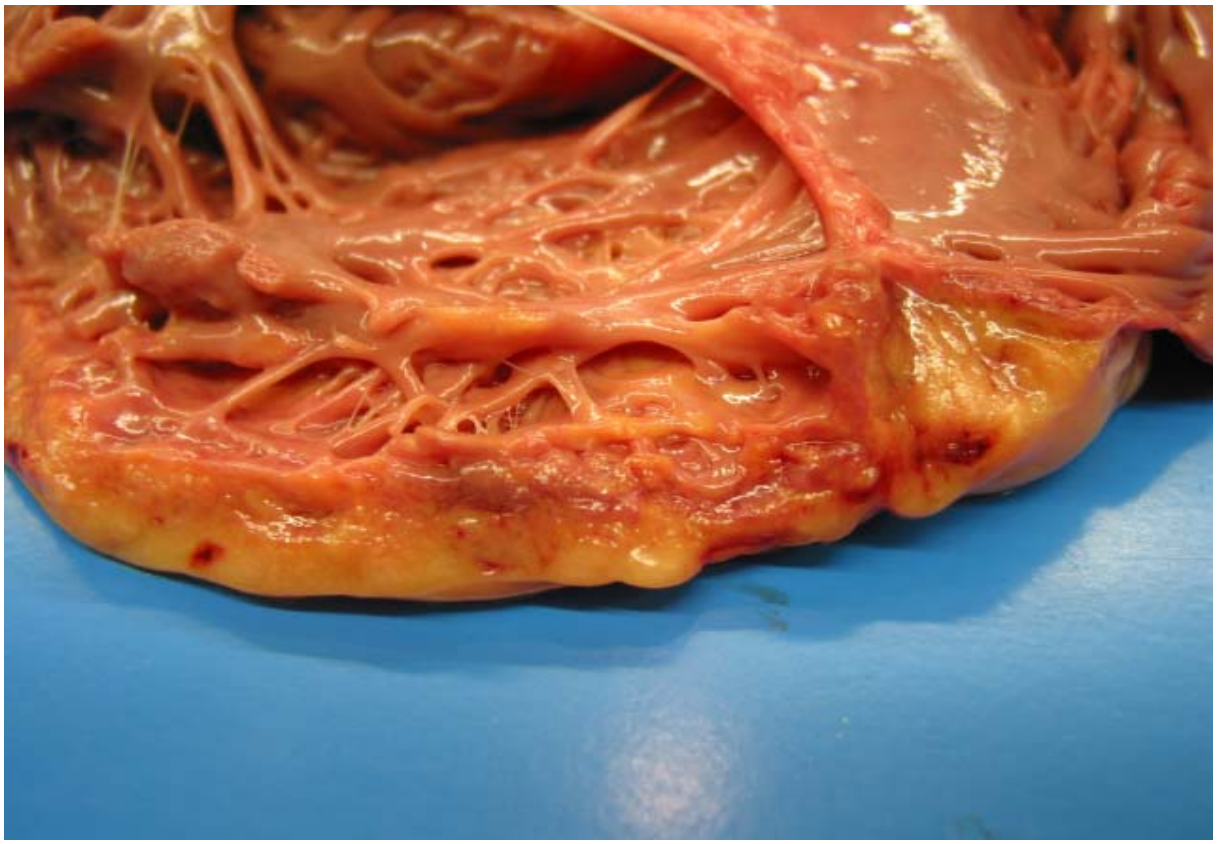
ARVC/D

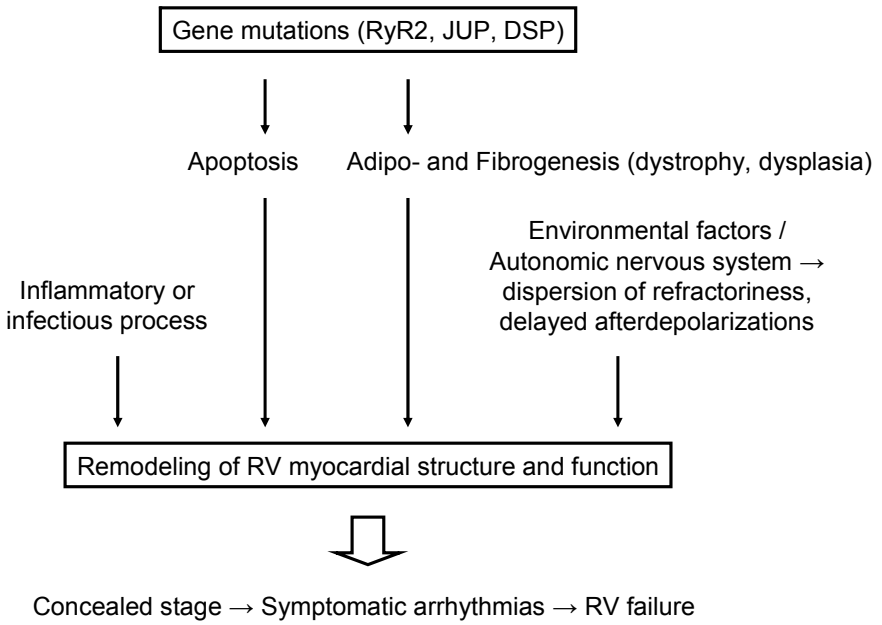
Ab. 1



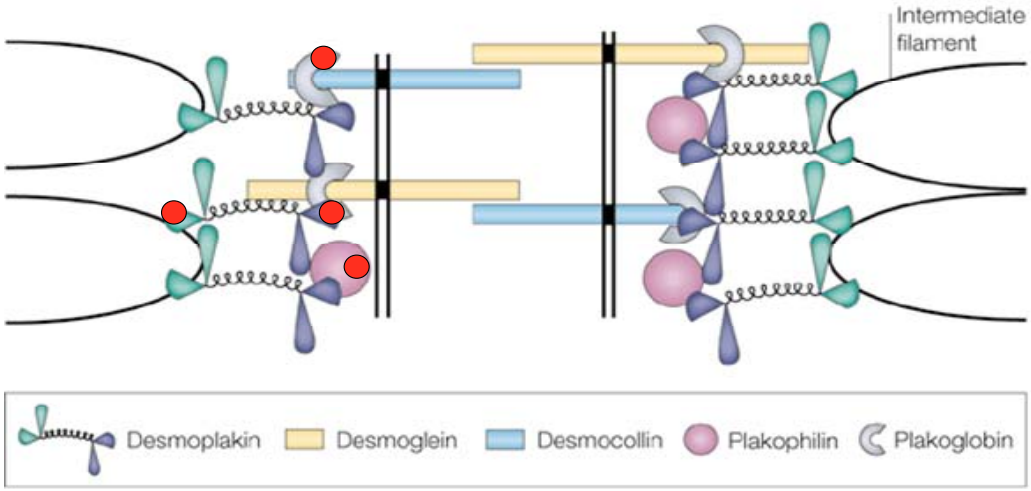
Ab. 2



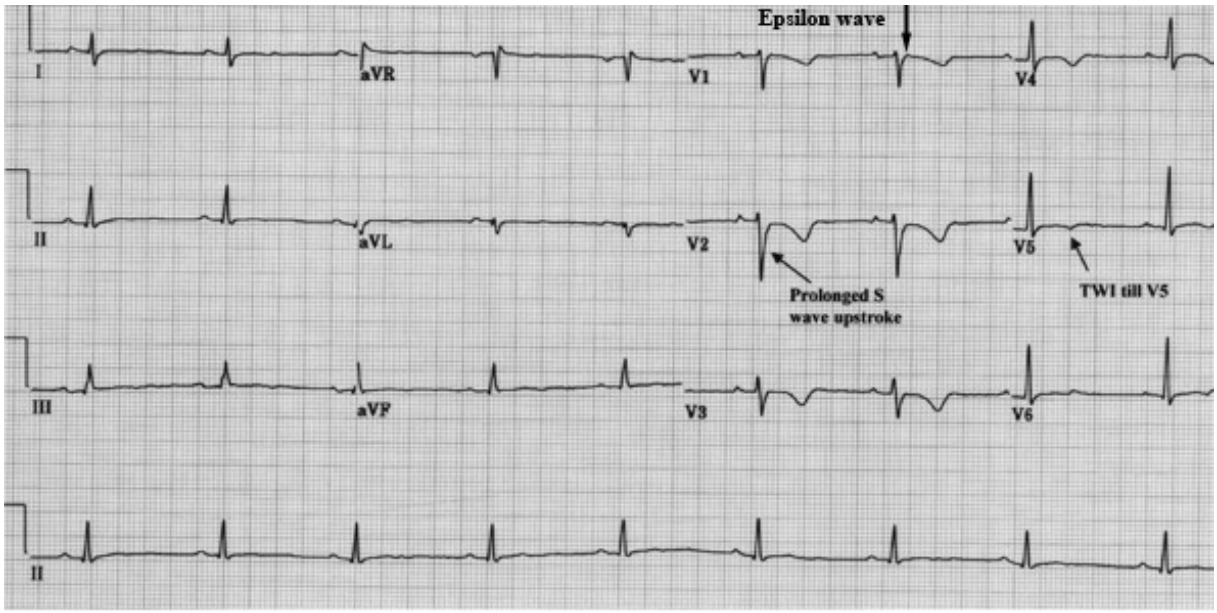
Ab. 3


Gene mutations (RyR2, JUP, DSP)
Apoptosis
Adipo- and Fibrogenesis (dystrophy, dysplasia)
Inflammatory or infectious process
Environmental factors / Autonomic nervous system → dispersion of refractoriness, delayed afterdepolarizations
Remodeling of RV myocardial structure and function
Concealed stage → Symptomatic arrhythmias → RV failure

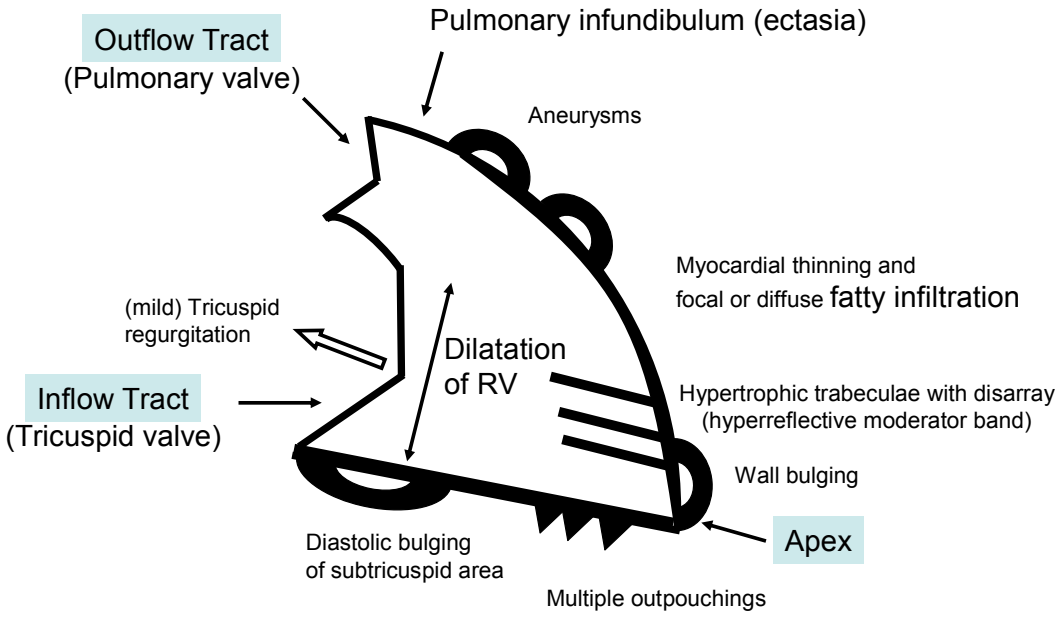
Ab. 4


Intermediate filament
Desmoplakin
Desmoglein
Desmocollin
Plakophilin
Plakoglobin

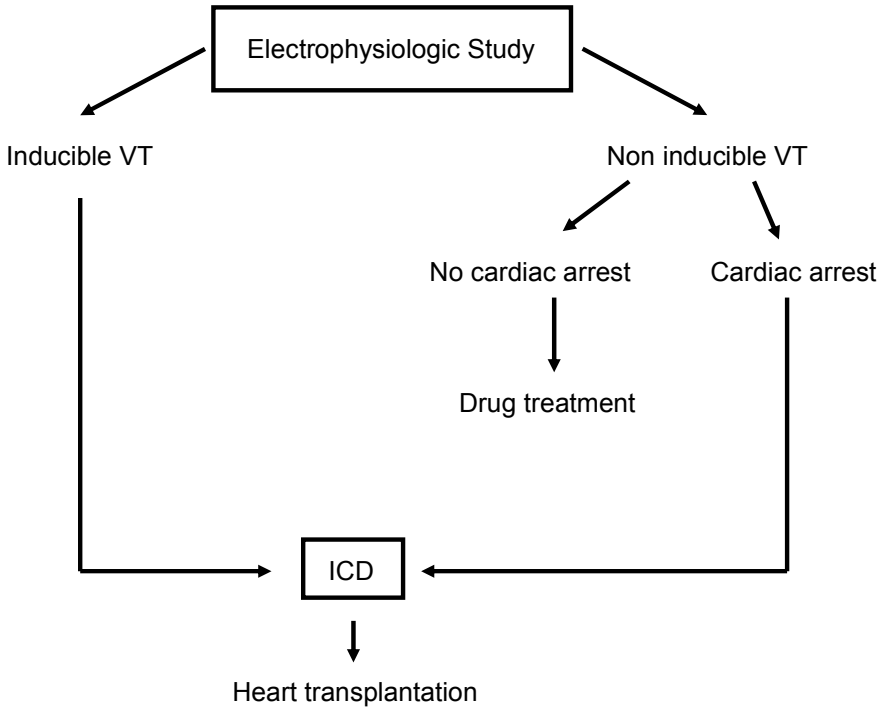
Ab. 5


Epsilon wave
I
aVR
V1
V4
II
aVL
V2
V5
Prolonged S wave upstroke
TWI till V5
III
aVF
V3
V6
II

Ab. 6


Outflow Tract
(Pulmonary valve)
Pulmonary infundibulum (ectasia)
Aneurysms
Myocardial thinning and
focal or diffuse fatty infiltration
(mild) Tricuspid
regurgitation
Dilatation
of RV
Inflow Tract
(Tricuspid valve)
Hypertrophic trabeculae with disarray
(hyperreflective moderator band)
Wall bulging
Apex
Diastolic bulging
of subtricuspid area
Multiple outpouchings

Ab. 7


Electrophysiologic Study
Inducible VT
Non inducible VT
No cardiac arrest
Cardiac arrest
Drug treatment
ICD
Heart transplantation